IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicants:	Jane Hirsh, Whe-Yong Lo, and Kamal K. Midha		
Serial No.:	09/858,016	Art Unit:	1616
Filed:	May 15, 2001	Examiner:	Gollamudi, Sharmila, S.
For:	*PHARMACEUTICAL COMPOSITION FOR BOTH INTRAORAL AND ORAL ADMINISTRATION*		

Commissioner for Patents
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SUBSTITUTE PRE-APPEAL BRIEF REQUEST FOR REVIEW

Please substitute this Argument In Support of the Pre-Appeal Brief Request for Review for the Argument In Support of the Pre-Appeal Brief Request for Review filed on July 19, 2006. A Notice of Appeal, a Request for a Pre-Appeal Brief Review, and the necessary fees were filed on July 19, 2006. Therefore, it is believed that no additional fee is required with this submission. However, should an additional fee be required, the Commissioner is hereby authorized to charge the fee to Deposit Account No. 50-3129.

ARGUMENTS

Claims 33-57 were rejected under 35 U.S.C. § 112, second paragraph, on the basis that the second oral portion is supposed to be released in the intestine and yet is capable of being chewed and swallowed. However, because the oral portion can be a delayed or sustained release formulation, and is swallowed, release will occur following passage through the stomach and in the intestine. Accordingly, even if the formulation is chewed and swallowed in the mouth, release occurs in the intestine. The Examiner also alleges that claim 1, 41, and 55 lack sufficient antecedent basis for the term "the core". Claim 1 is canceled. It is assumed that the Examiner is referring to claim 33. Applicants will amend claims 33, 41, and 55 to define a core or to define the intraoral portion as a film coating or compression coating which is applied to the second oral portion, if necessary. The Examiner also alleges that "comprises one or more of the outer layers" in claim 37 lack sufficient antecedent basis. This objection is unclear. Claim 37 depends from claim 35, which defines the composition of claim 33 in the form of a tablet or capsule unit dosage form. Claim 37 defines the tablet of claim 33 as a multilayer tablet, wherein the oral component comprises one or more inner layers of the tablet and the intraoral component comprises one or more outer layers of the tablet. The antecedent basis is inherent in the claim itself.

Claims 41, 51, and 54 were rejected under 35 U.S.C. § 103(a) over GB 800,973 to Sterling ("Sterling") in view of Remington's Pharmaceutical Sciences, 18th Ed. (1990), page 844, optionally in view of U.S. Patent No. 3,898,323 to Fennell et al. ("Fennell").

Sterling describes a multi-layered pill or tablet having a medicinal core and an intervening taste-indicating alarm layer or lamination, this having an outer medicinal layer soluble in the mouth. Sterling does not disclose a pharmaceutical composition comprising a pharmaceutically acceptable effervescent agent which generates effervescence or a pharmaceutically acceptable signaling system, **located between the first intraoral component and the second oral component**, which is detectable by the patient upon substantial release of the pharmaceutically active ingredient in the first intraoral component when contacted with salivary fluid. Sterling also does not disclose a composition where the intraoral portion is a film coating applied to the core or a compression coating compressed around the core.

Remington states that nitroglycerin has a molecular weight of 227.09 and that the dose of nitroglycerin is 1 mg and 0.15-0.6 mg for buccal tablets and sublingual tablets, respectively. Fennell describes a composition for rendering sour tasting foods sweet tasting comprising miraculin glycoprotein obtained from the ripe fruit of *Synsepalum dulcificum* and a non-toxic alkaline material. The composition is placed in the mouth 1-2 hours before ingesting sour food.

Remington and Fennell do not disclose the claim elements missing from Sterling. One of ordinary skill in the art would not be motivated to combine Sterling and Remington with Fennell because Fennell describes a taste masking composition which is ingested before ingesting sour-tasting foods. The taste masking composition neutralizes mouth acids and coats the tongue. Fennell does not disclose or suggest coating a composition containing an intraoral component and an oral component as defined in claims 41, 51, and 54.

Claims 33-39, 41-50, and 51-56 were rejected under 35 U.S.C. § 103(a) over Sterling in view of U.S. Patent No. 6,140,319 to Powell et al. ("Powell", DE 3338978 to Frömming ("Frömming"), and U.S. Patent No. 3,898,323 to Fennell et al. ("Fennell").

Sterling is discussed above. Sterling does not disclose a pharmaceutical composition comprising a first intraoral portion which rapidly dissolves or disintegrates intraorally to release a therapeutically effective amount of at least one pharmaceutically active ingredient which is absorbed through the buccal or sublingual mucosa (by virtue of having a sufficient resonance time and sufficiently low molecular weight) for uptake in the oral cavity in a therapeutically effective level, wherein the active ingredient is as defined in claim 33. Sterling fails to disclose a second component which is either chewable or provides sustained release. Sustained release is where the drug is released over an extended period of time, for example 0.5 to 24 hours (page 23, lines 21-26). Delayed release is not the same as sustained release. Sterling does not disclose a composition wherein the intraoral portion is a film coating or a compression coating. Sterling describes compositions wherein the intraoral portion is **dusted** onto the core. Powell describes the use of one or more vasopeptidase inhibitors to treat and/or relieve the symptoms of angina pectoris. Frömming describes the use of verapamil or gallopamil for sublingual or buccal administration administered in a tablet, a chewable capsule or a spray. Fennell is discussed above. Novelty has been established.

There is no motivation to combine or modify as required to arrive at the claimed compositions; therefore claims 33-39, 41-50, and 51-56 are not obvious over Sterling in view of Powell, Frömming, and Fennell.

Claims 33-36, 38-39, 43-44, 47-49, 52-53, and 55-56 were rejected under 35 U.S.C. § 103(a) over U.S. Patent App.Pub. No. 2001/0002999 to Neuser in view of U.S. Patent No. 4,661,492 to Lewis et al. ("Lewis") in further view of U.S. Patent No. 5,686,122 to Liedtke ("Liedtke").

Neuser describes pharmaceutical compositions which can be administered orally and contain a fixed combination of at least one ***locally*** acting analgesic with a rapid onset of action and at least one ***systemically*** acting analgesic with a sustained action. Lewis describes an analgesic composition in parenteral or sublingual unit dosage form comprising an active dose of buprenorphine and an amount of naltrexone sufficient to prove aversive to a narcotic addict by parenteral administration but insufficient to compromise the analgesic action of the buprenorphine. Liedtke describes single dosage topical pharmaceutical formulations. The references do not disclose each and every element of the claims. The claimed compositions contain an intraoral and oral active agent for systemic administration. Lewis and Liedtke do not provide the elements missing from Neuser. Further, one of ordinary skill in the art would not be motivated to combine the references as Liedtke disclose **topical** formulations, not oral formulations as defined in the claims. Accordingly, claims 33-36, 38-39, 43-44, 47-49, 52-53, and 55-56 are not obvious over Neuser in view of Lewis and Liedtke.

Claims 33-36, 38-40, 42-44, 47-48, 52-53, and 55-56 were rejected under 35 U.S.C. § 103(a) as being unpatentable over WO 00/35296 to Johnson ("Johnson").

Johnson describes a coated chewing gum, wherein the coating contains a medicament or active agent for systemic delivery upon chewing. The core of the chewing gum can also contain an active agent. The claimed compositions contain an intraoral portion that rapidly dissolves or disintegrates immediately upon administration. It is not chewed as in Johnson. Johnson does not disclose a second oral formulation that is sustained release or chewable. The claimed compositions are designed to be swallowed once the intraoral layer has disintegrated. Chewing gum is not normally swallowed. John does not disclose the composition of claim 33 in the form of a

capsule or tablet (claims 35-36 and 38-39). Accordingly, claims 33-36, 38-40, 42-44, 47-48, 52-53, and 55-56 are not obvious in view of Johnson.

Claim 57 was rejected under 35 U.S.C. § 103(a) over Johnson in view of U.S. Patent No. 5,310,561 to Jao et al. ("Jao").

Claim 57 depends from claim 55 which defines a process for the preparation of a composition containing a first intraoral portion and a second oral portion, wherein the second oral component is a tablet core or at least one layer of a multi-layer tablet or an uncoated capsule. Johns describes chewing gums, not capsules or tablets. Jao describes a dosage form containing a wall that surrounds a lumen comprising the drug, a driving means for delivering the drug, and a rate controlled exit means. One of ordinary skilled in the art would not be motivated to combine the chewing gums of Johnson with the dosage form described in Jao. The references, in combination, do not disclose each and every element of claim 57 nor the motivation to combine.

Claims 33-43 and 49-57 were rejected under 35 U.S.C. § 103(a) over U.S. Patent No. 5,053,032 to Barclay et al. ("Barclay") in view of U.S. Patent No. 6,200,604 to Panther et al. ("Panther").

Barclay describes an ***osmotic*** device for a delivering a drug into the mouth of a human patient (abstract). The device comprises a wall surrounding a compartment housing, a layer of an agent insoluble to very soluble in aqueous biological fluids such as saliva and a layer of fluid swellable hydrophilic polymer. A passageway in the wall connects the agent with the exterior of the device. The agent is released from the device by the combined actions of fluid being imbibed through the wall into the compartment producing a solution or suspension containing agent and by fluid being imbibed by the hydrophilic polymer causing it to expand and increase in volume, thereby exerting a force against the solution or suspension which is pushed through the passage way. Example 3 describes an osmotic device containing an overcoat of ibuprofen and HPMC. The overcoat layer is completely removed in 15-30 minutes. The claimed compositions contain an intraoral portion which rapidly dissolves after coming in contact with the patient's saliva. The active agent in the oral portion is released due to dissolution of the carrier or degradation of the sustained release matrix. It is not released by being pushed out a passageway drilled through the core as described in Barclay. Panther describes a pharmaceutical dosage form comprising an orally administerable

medicament in combination with an effervescent agent used as a penetration enhancer to influence the permeability of the medicament across the buccal, sublingual, and gingival mucosa (col. 2, lines 7-11). Panther discloses that the effervescent agent can act to increase the rate and extent of absorption of the active agent by: (1) reducing the mucosal layer thickness and/or viscosity; (2) tight junction alteration; (3) inducing a change in the cell membrane structure; and (4) increasing the hydrophobic environment within the cellular membrane. One of ordinary skill in the art would not be motivated to combine Barclay and Panther to arrive at the claimed compositions. Barclay described devices where the drug is release by being pushed put a passageway, which is drilled into the core of the device. Panther describes effervescent agents act to increase the rate and extent of absorption. Accordingly, claims 33-43 and 49-57 are not obvious over Barclay in view of Panther.

For the foregoing reasons, Appellant submits that claims 1-4, 6-12, 14-26, and 38 are patentable.

Respectfully submitted,

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